

Applicants: Michael J. Elliott, et al.  
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82 37. (Thrice Amended) The method of claim 34, wherein the chimeric antibody is monoclonal antibody cA2.

#### **REMARKS**

Claims 6, 8-10, 12-15, 29-32 and 34-37 are pending and under examination in the subject application. Applicants have amended claims 15 and 37 in order to introduce certain format changes. Applicants maintain that these amendments raise no issue of new matter, and respectfully request entry of this Amendment. Upon entry of this Amendment, claims 6, 8-10, 12-15, 29-32 and 34-37 will still be pending and under examination.

Pursuant to the requirements of 37 C.F.R. 1.121(b)(2), applicants annex hereto as Exhibit A claims 15 and 37 marked up to show the changes made herein relative to the previous version of those claims.

In view of the arguments set forth below, applicants maintain that the Examiner's objections and rejections made in the October 3, 2000 Office Action have been overcome, and respectfully request that the Examiner reconsider and withdraw same.

#### **The Claimed Invention**

This invention provides methods of treating or preventing thrombosis, and decreasing plasma fibrinogen. These methods comprise administering a tumor necrosis factor antagonist to a subject diagnosed as suffering from or at risk of thrombosis.

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This invention is based on applicants' *surprising discovery* that inhibiting the biological activity of TNF $\alpha$  reduces fibrinogen levels in subjects suffering from or at risk of thrombosis. Since fibrinogen plays an integral role in forming thrombi, this invention has considerable use for treating and preventing thrombosis in subjects diagnosed as suffering from or at risk thereof.

**Rejection Under 35 U.S.C. §112, Second Paragraph**

The Examiner rejected claims 15 and 37 under 35 U.S.C. §112, second paragraph.

The Examiner maintains as indefinite the language of claims 15 and 37, which depend on claims 14 and 36, respectively, and recite "wherein the chimeric antibody is the monoclonal antibody cA2".

In response, applicants point out that claims 15 and 37 now depend from claims 12 and 34, respectively.

In view of the above remarks, applicants maintain that claims 15 and 37 satisfy the requirements of 35 U.S.C. §112, second paragraph.

**Rejection Under 35 U.S.C. §102(a)**

The Examiner rejected claims 6, 8, 10, 12-15, 29, 30, 32 and 34-37 under 35 U.S.C. §102(a) as allegedly anticipated by Hommes, et al. (Gastroenterology, 1995, Vol. 108, No. 4, suppl., p. A838) as

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"evidenced" by Leardi, et al. (Italian Journal of Surgical Sciences, 1983, Vol. 13, pp. 197-201) and Le, et al. (U.S. Patent No. 5,919,452).

In response to the Examiner's rejection, applicants respectfully traverse.

Briefly, claims 6, 8, 10, 12-15, 29, 30, 32 and 34-37 provide methods of treating or preventing thrombosis and decreasing plasma fibrinogen in a subject diagnosed as suffering from or at risk of thrombosis. These methods comprise administering to the subject a therapeutically effective amount of a TNF antagonist.

To anticipate the claimed method, Hommes, et al. would have to teach each and every element thereof. They fail to do this.

Instead, Hommes, et al. teach that the treatment of *Crohn's disease* patients with chimeric monoclonal antibody cA2 decreases "thrombin generation" and "endothelial activation-markers". Hommes, et al. do not teach the treatment or prevention of thrombosis, nor do they teach a decrease of plasma fibrinogen levels. In fact, nowhere do Hommes, et al. even mention the terms "thrombosis" and "plasma fibrinogen".

Leardi, et al. do nothing to cure this shortcoming. Though they disclose that Crohn's disease patients are at risk of suffering from thrombosis and hyperfibrinogenemia, Leardi, et al. do not teach the use of TNF antagonists to decrease either of these two conditions. In fact nowhere do Leardi, et al. even mention the

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treatment of Crohn's disease, or more specifically, thrombosis and elevated plasma fibrinogen levels, with any TNF antagonists.

Le, et al. also do not cure the shortcoming of Hommes, et al. Le, et al. disclose the treatment of certain TNF $\alpha$ -mediated diseases with chimeric monoclonal antibody cA2 and antibodies which compete therewith. Le, et al. do not teach the use of these antibodies to treat or prevent thrombosis, or to decrease plasma fibrinogen levels.

For these reasons, Hommes, et al., as "evidenced" by Leardi, et al. and Le, et al., fail to teach each and every element of the rejected claims.

In view of the above remarks, applicants maintain that claims 6, 8, 10, 12-15, 29, 30, 32 and 34-37 satisfy the requirements of 35 U.S.C. §102(a).

**Rejection Under 35 U.S.C. §102(b)**

The Examiner rejected claims 6 and 8 under 35 U.S.C. §102(b) as allegedly anticipated by Arii, et al. (Circulation, 1994, Vol. 90, No. 4, part 2, p. I522, abstract No. 2811), Verteas, et al. (ASAIO Journal, 1994, Vol. 40, pp. M554-M559), or Wakefield, et al. (Arteriosclerosis, Thrombosis and Vascular Biology, 1995, Vol. 15, pp. 258-268).

In response to the Examiner's rejection, applicants respectfully traverse, and maintain that each of the above cited references

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fails to teach each and every element of the rejected claims.

The rejected claims are discussed above.

Arii, et al. provide data suggesting that TNF may induce myocardial slippage after myocardial infarction. However, Arii, et al. do not teach a method of treating or preventing any disorder in a subject, and in particular, do not teach the treatment or prevention of thrombosis. Indeed, nowhere do Arii, et al. mention the term thrombosis.

Vertees, et al. teach that anti-TNF $\alpha$  monoclonal antibody pre-treatment in the swine model of cardiopulmonary bypass (CPB) reduces CPB-associated leukocyte changes and may help ameliorate clinical manifestations of post-pump inflammatory response syndrome. Vertees, et al. disclose that one of the possible post-operative effects of post-pump inflammatory response syndrome is "coagulopathy", or disease affecting blood coagulation. Vertees, et al. do not teach a method of treating or preventing thrombosis in a subject diagnosed as suffering from or at risk of thrombosis. Moreover, Vertees, et al. do not specify thrombosis as a coagulopathy, nor do they even mention the term thrombosis.

Wakefield, et al. teach that anti-TNF antibodies partially reduce vein wall neutrophil extravasation, and thus partially inhibit the vein wall inflammatory response which occurs as a result of venous thrombosis. Wakefield, et al. suggest that a decrease in the vein wall inflammatory response may result in a decline in the manifestations of chronic venous insufficiency, a syndrome which

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occurs after venous thrombosis. However, Wakefield, et al. do not teach the treatment or prevention of thrombosis itself.

Therefore, Arii, et al., Vertees, et al. and Wakefield, et al. all fail to teach each and every element of the rejected claims.

In view of the above remarks, applicants maintain that claims 6, 8-10, 12-15, 29-32 and 34-37 satisfy the requirements of 35 U.S.C. §102(e).

Rejections Under 35 U.S.C. §103(a)

The Examiner rejected claims 6, 8, 9, 29, 30 and 31 under 35 U.S.C. §103(a) as allegedly unpatentable over Hommes, et al. as "evidenced" by Leardi, et al. and Le, et al. in view of Dhainaut, et al. (Critical Care Medicine, 1995, Vol. 13, pp. 197-201).

In response to the Examiner's rejection, applicants respectfully traverse, and maintain that the Examiner has failed to establish a *prima facie* case of obviousness.

Again, claims 6, 8 and 9 provide a method of treating or preventing thrombosis. Claims 29, 30 and 31 provide a method of decreasing plasma fibrinogen. The methods of claims 6, 8, 9, 29, 30 and 31 comprise administering a TNF antagonist to a subject diagnosed as suffering from or at risk of thrombosis. The TNF antagonist can be an anti-TNF antibody or antigen-binding fragment thereof.

The methods of this invention are based on the surprising discovery

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that inhibiting the biological activity of TNF $\alpha$  reduces fibrinogen levels in subjects suffering from or at risk of thrombosis. Since fibrinogen plays an integral role in forming thrombi, this invention has considerable use for treating and preventing thrombosis in subjects diagnosed as suffering from or at risk thereof.

To establish a *prima facie* case of obviousness, the Examiner must demonstrate three things with respect to each claim. First the cited references, when combined, must teach or suggest every element of the claims. Second, one of ordinary skill must have been motivated to combine the teachings of the cited references at the time of the invention. Third, there must be a reasonable expectation that the claimed invention would succeed.

Here, the cited references fail to support a *prima facie* case of obviousness. Specifically, to support a *prima facie* case of obviousness, the teachings of Hommes, et al., as evidenced by Leardi, et al. and Le, et al. in view of Dhainaut, et al., would have to teach or suggest every element of the claims. Hommes, et al., Leardi, et al. and Le, et al. are discussed above.

Again, Hommes, et al. do not teach the treatment or prevention of thrombosis, or a decrease of plasma fibrinogen levels, nor do they mention the terms "thrombosis" and "plasma fibrinogen".

Combining Hommes, et al. with Dhainaut, et al. does not cure this deficiency. Dhainaut, et al. teach the treatment of *septic shock* with an anti-TNF antibody. Dhainaut, et al. do not teach treatment

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or prevention of thrombosis, or the decrease of elevated fibrinogen levels.

Moreover, these references, when combined, would also have to motivate one of ordinary skill to combine their teachings at the time of the invention. The mere use of TNF antagonists for the treatment or prevention of diseases generally, and Crohn's disease or sepsis/septic shock specifically, does not suggest or motivate one to use TNF antagonists in the treatment or prevention of other distinct diseases or conditions, such as thrombosis or elevated fibrinogen levels.

Applicants' invention is based on the surprising discovery that inhibiting TNF $\alpha$  activity reduces fibrinogen levels in subjects suffering from or at risk of suffering from thrombosis. At the time of this application, this unexpected finding was unknown to those skilled in the art. Ignoring this fact, however, the Examiner makes an impermissible leap by asserting that the successful use of TNF antagonists against Crohn's disease and sepsis/septic shock is predictive of success against wholly distinct diseases or conditions such as thrombosis.

In light of these teachings and their shortcomings, the Examiner has failed to show that the cited references - four in all - teach or suggest every element of the claims, or would have motivated one of ordinary skill to combine them. To maintain otherwise would be hindsight.

Accordingly, the Examiner has failed to establish the *prima facie*



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obviousness of claims 6, 8, 9, 29, 30 and 31 over Hommes, et al. as "evidenced" by Leardi, et al. and Le, et al. in view of Dhainaut, et al. For the same reasons, applicants alternatively maintain that the rejected claims would not have been obvious over these references.

The Examiner also rejected claims 6 and 8 under 35 U.S.C. §103(a) as allegedly unpatentable over Fisher, et al. (Critical Care Medicine, 1993, Vol. 21, pp. 318-327) in view of Hooper, et al. (Blood, 1994, Vol. 84, pp. 483-489) or Jolin, et al. (Acta Anaesthesiologica Scandinavica, Supplementum, 1991, Vol. 95, pp. 40-52).

In response to the Examiner's rejection, applicants respectfully traverse, and maintain that the Examiner has failed to establish a *prima facie* case of obviousness.

The rejected claims are discussed above.

Here, the cited references fail to support a *prima facie* case of obviousness. First, Fisher, et al. in view of Hooper, et al. or Jolin, et al. fail to teach or suggest every element of the claims.

Fisher, et al. teach the treatment of severe sepsis with anti-TNF monoclonal antibody. This reference is not directed to thrombosis.

Hooper, et al. do not cure this defect. Hooper et al. teach that treatment with anti-TNF $\alpha$  antibodies can, via an as yet unknown mechanism, reverse the inhibitory effect of TNF on protein S

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levels. Hooper, et al. offer no data or other evidence that anti-TNF $\alpha$  antibody treatment reduces or prevents thrombosis. Indeed, Hooper, et al. acknowledge that the correlation between protein S deficiency and thrombosis is "not well documented".

Jolin, et al. also do not cure the deficiencies of Fisher, et al. Jolin, et al. teach methods aimed at reducing hypoxic pulmonary vasoconstriction (HPV) in the treatment of adult respiratory distress syndrome (ARDS). A large number of different ARDS mediators and vasoconstrictive agents were examined for their potential for inhibiting HPV, none of which could be classified as TNF antagonists.

In light of these teachings and their shortcomings, the Examiner has failed to show how the cited references teach or suggest every element of the claims.

Second, these references, when combined, would not have motivated one of ordinary skill to combine their teachings. This lack of motivation is due to the reasons set forth above concerning the surprising nature of this invention.

In light of these teachings and their shortcomings, the Examiner has failed to show that the cited references would have motivated one of ordinary skill to combine them. To maintain otherwise would be hindsight.

Accordingly, the Examiner has failed to establish the *prima facie* obviousness of claims 6 and 8 over Fisher, et al. in view of

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Hooper, et al. or Jolin, et al. For the same reasons, applicants alternatively maintain that the rejected claims would not have been obvious over these references.

The Examiner also rejected claims 6, 8, 10, 12-15, 29, 30, 32 and 34-37 under 35 U.S.C. §103(a) as allegedly unpatentable over Le, et al. (U.S. Patent No. 5,656,272) in view of Hooper, et al. or Jolin, et al.

In response to the Examiner's rejection, applicants respectfully traverse, and maintain that the Examiner has failed to establish a *prima facie* case of obviousness.

The references and rejected claims are discussed above.

Here, the cited references fail to support a *prima facie* case of obviousness.

First, Le, et al. in view of Hooper, et al. or Jolin, et al. fail to teach or suggest every element of the claims. Again, Le, et al. teach the treatment of Crohn's disease with chimeric monoclonal antibody cA2 and antibodies which compete therewith. Le, et al. do not teach the use of these antibodies to treat or prevent thrombosis, or to decrease plasma fibrinogen levels.

Neither Hooper, et al. nor Jolin, et al. cure this defect for the reasons discussed above.

Second, these references, when combined, would not have motivated

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one of ordinary skill to combine their teachings for the reasons set forth above.

In light of these teachings and their shortcomings, the Examiner has failed to show how the cited references teach or suggest every element of the claims, or would have motivated one of ordinary skill to combine them. To maintain otherwise would be hindsight.

Accordingly, the Examiner has failed to establish the *prima facie* obviousness of claims 6, 8, 10, 12-15, 29, 30, 32 and 34-37 over Le, et al. in view of Hooper, et al. or Jolin, et al. For the same reasons, applicants alternatively maintain that the rejected claims would not have been obvious over these references.

In view of the above remarks, applicants maintain that claims 6, 8, 10, 12-15, 29, 30, 32 and 34-37 satisfy the requirements of 35 U.S.C. §103(a).

#### **Summary**

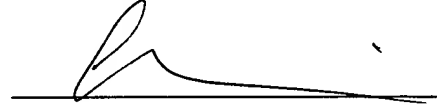
In view of the amendments and remarks made herein, applicants maintain that the claims pending in this application are in condition for allowance. Accordingly, allowance is respectfully requested.

If a telephone interview would be of assistance in advancing the prosecution of the subject application, applicants' undersigned attorneys invite the Examiner to telephone them at the number provided below.

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No fee is deemed necessary in connection with the filing of this Amendment. However, if any fee is required, authorization is hereby given to charge the amount of such fee to Deposit Account No. 03-3125.

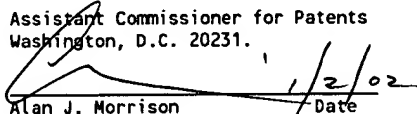
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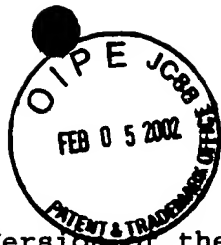
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1/2/02  
Date



Marked-Up Version of the Amended Claims

15. (Thrice Amended) The method of claim [14] 12, wherein the chimeric antibody competitively inhibits binding of TNF $\alpha$  to monoclonal antibody cA2.
  
37. (Thrice Amended) The method of claim [36] 34, wherein the chimeric antibody is monoclonal antibody cA2.